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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/091,591
Filing Date: March 07, 2002
Appellant(s): BERGERON, RAYMOND J.

Gianna J. Arnold
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 9/26/2008 appealing from the Office action mailed 2/27/2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

A substantially correct copy of appealed claims 1-6 appears on pages A-i and A-ii of the Appendix to the appellant's brief. The minor errors are as follows: in claim 1, there is a typographical error in the definition of Q. In the amendment filed 11/26/2007, Appellants amended the definition of Q to recite "a cycloalkyl group having **5** to 10 carbon atoms". In the

Appendix of Claims, claim 1 recites ""a cycloalkyl group having 3 5 to 10 carbon atoms". The "3" was deleted in the claim amendments filed 11/26/2007.

(8) Evidence Relied Upon

5,889,061	Frydmann et al.	03-1999

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are again rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

No support is seen in the specification for the *proviso*, "excluding the *trans* isomers of the compounds having the structures...." as recited in claim 1. The first excluded compound is CHX(3,4,3-*trans*), which is positively recited at pages 8 and 14 of the specification. This is the **only** specific compound identified in the specification. The second excluded compound is CHX(4,4,4-*trans*), which is neither positively nor negatively recited in the specification. Accordingly, Applicant has no written basis for the specific exclusion of CHX(4,4,4-*trans*) from the claims.

Claims 1-6 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

In the amendment to the claims filed 11/26/2007, claim 1 was amended to recite the limitation wherein "Q is a cycloalkyl group having from 5 to 10 carbon atoms". Previously presented claim 1 had the limitation wherein Q is a cycloalkyl group having from 3 to 10 carbon atoms. No support is found in the originally filed disclosure for cycloalkyl groups having from 5 to 10 carbon atoms as recited in the instant claims. The only specific compound disclosed contains a cyclohexyl group (*i.e.*, 6 carbon atoms). There are no compounds recited in the original disclosure that would provide support for the limitation of Q being a cycloalkyl group having from 5 to 10 carbon atoms.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Frydman *et al***. (U.S. Patent No. 5,889,061; Issued Mar. 30, 1999).

The instant claims recite pharmaceutical compositions comprising an effective amount of a compound having the formula:

$$R_1\text{-}N^1(R_2)\text{-}(CH_2)_x\text{-}N^2H\text{-}Q\text{-}N^3H\text{-}(CH_2)_y\text{-}N^4(R_3)\text{-}R_4 \qquad (I)$$

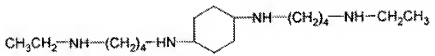
wherein: R_1, R_2, R_3 and R_4 are the same or different and are H, alkyl, cycloalkyl or aralkyl having from 1 to 12 carbon atoms, or a heterocyclic group having from 3 to 10 atoms wherein the hetero atom is said N^1 or N^4;

Q is a cycloalkyl group having from 3 to 10 carbon atoms;

x is an integer from 3 to 6, inclusive;

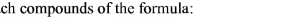
excluding the *trans* isomers of the compounds having the structures:

and



and a pharmaceutically acceptable carrier. Instant claim 3 recites the limitation wherein Q is cyclohexyl in the compounds of Formula I. Claim 6 recites the limitation wherein Q is cyclohexyl; x and y are 3; R_1 and R_3 are both H, and R_2 and R_4 are both ethyl. Other dependent claims recite limitations wherein: Q is connected either *cis* or *trans* as the (1,2), (1,3), (1,4), (1,5) or (1,6) isomer (claim 2); x is 3 and y is 3 (claim 4); and x is 3, y is 3, R_1 and R_3 are both H and R_2 and R_4 are both ethyl (claim 5).

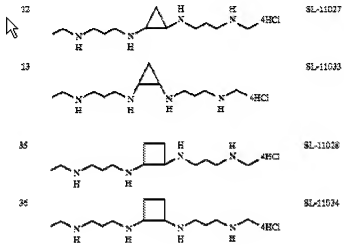
Frydman *et al.* teach compounds of the formula:



E-NH-D-NH-B-A-B-NH-D-NH-E ①

wherein A is C_2–C_4 alkene, C_3–C_6 cycloalkyl, cycloalkenyl, or cycloaryl; B is independently a single bond, C_1–C_4 alkyl alkenyl; D is independently C_1–C_6 alkyl or alkenyl, or C_3–C_6 cycloalkyl, cycloalkenyl, or cycloaryl; and E is independently H, C_1–C_3 alkyl or alkenyl; and

and pharmaceutically acceptable salts thereof (Abstract; col. 2, lines 1-11). Exemplified compounds of the invention are taught in Table 1.



Instant claim 2 recites the limitation wherein Q is connected either *cis* or *trans* as the (1,2) isomer. The above compounds are connected *cis* (SL-11033 and SL-11034) and *trans* (SL-11027 and SL-11028) as the (1,2) isomer, thus teaching the limitations of claim 2.

Pharmaceutical compositions comprising the compounds of the invention in a pharmaceutically acceptable carrier and in an effective amount are taught at column 21, line 3 to column 22, line 9. For example, Frydman *et al.* teach formulating the compounds of the invention in pharmaceutically acceptable carriers (col. 21, lines 35-44 and lines 52-55).

It is well established that intended use does not impart patentability in a composition claim. See *In re Zierden*, 411 F.2d 1325, 1329, 162 USPQ 102, 104 (CCPA 1969):

> A mere statement of a new use for an otherwise old or obvious composition cannot render a claim to the composition patentable. As we said in *In re Lemin*, 51 CCPA 942,326 F.2d 437,140 USPQ 273,276 (1964),
>
> > Appellants are clearly correct in demanding that the subject matter as a whole must be considered under 35 U.S.C. 103. But in applying the statutory test, the differences over the prior art must be more substantial than a statement of the intended use of an old composition. ... It seems to us that the composition ... would be exactly the same whether the user were told to cure pneumonia in animals with it ... or to promote plant growth with it (as here). The directions on the label will not change the composition....

See also, *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("[t]the discovery of a new property or use of a previously known composition, even when that property and use are unobvious from the prior art, cannot impart patentability to claims to the known composition"). Accordingly, the claims simply require a composition comprising a compound of formula I and a pharmaceutically acceptable carrier. As such, the compositions of Frydman *et al*. render *prima facie* obvious the instantly claimed compositions.

Frydman *et al*. differ from the instant claims in that they do not explicitly exemplify compounds wherein the C_3-C_6 cycloalkyl is cyclohexyl. Exemplified compounds of the invention are drawn to cyclopropyl and cyclobutyl moieties (Table 1). However, Frydman *et al*. teach that "A" (Q in the instant claims) can be C_2-C_6 alkene, C_3-C_6 cycloalkyl, cycloalkenyl, or cycloaryl (Abstract). Thus, with respect to cycloalkyl groups, there are only four possible substitutions: cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The inventors made and exemplified cyclopropyl and cyclobutyl substituted compounds (Table 1) having identical substituents as those recited in instant claim 6 (*i.e*., x and y are 3; R_1 and R_3 are both H, and R_2 and R_4 are both ethyl).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Scope and Content of the Prior Art:

In the instant case, Frydman *et al.* teach a genus of compounds having a limited number of alternate substitutions. With respect to the instantly claimed sub genus of compounds having a cyclohexyl group, Frydman *et al.* teach that the compounds of the invention can be substituted with a C_3-C_6 cyclohexyl (four possible substitutions). The compounds of Frydman *et al.* are taught to be useful in the treatment of cancer. In this regard, compounds having a cyclopropyl (C_3) and cyclobutyl (C_4) substitution were exemplified and tested for anticancer activity (Table 1 and Table 2). The number of species encompassed by the genus taught in Frydman *et al.* is relatively small. For example, there are only twelve possible substitutions for A, eight for B, eighteen for D, and thirteen for E. The majority of these substitutions are structurally related and represent homologous series (*e.g.*, C_2-C_6 alkene, C_3-C_6 cycloalkyl, C_1-C_6 alkyl, etc.).

Differences Between Prior Art and Claims:

The closest disclosed prior art species to the sub genus instantly claimed are the compounds designated SL-11027, SL-11033, SL-11028, and SL-11034 in Frydman *et al.* (Table

1). These species differ from the instantly claimed genus **only** in the number of carbons present in the cycloalkyl substitution (*i.e.*, C_3 and C_4 versus C_6); all other substituents are identical.

Level of Ordinary Skill in the Art:

A person having ordinary skill in the art at the time of the present invention would generally be a medical chemist well practiced in the art of structure-activity relationships as they pertain to chemical modifications and biological activity.

Objective Evidence and Motivation:

In light of the above findings relating to the three *Graham* factors, the skilled artisan would have been motivated to make the claimed sub genus of compounds and to formulate them in a pharmaceutical composition. See, *e.g.*, *Deuel*, 51 F.3d at 1557, 34 USPQ2d at 1214 ("[A] *prima facie* case of unpatentability requires that the teachings of the prior art suggest *the claimed compounds* to a person of ordinary skill in the art." (emphasis in original)); *In re Lalu*, 747 F.2d 703, 705, 223 USPQ 1257, 1258 (Fed. Cir. 1984) ("The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound."). Considering the size of the prior art genus, especially with respect to the limited number of cycloalkyl groups contemplated by Frydman *et al.*, one skilled in the art could readily envisage each member of the sub genus of compounds containing C_3-C_6 cycloalkyl groups. *In re Petering*, 301 F.2d 676, 681, 133 USPQ 275, 280 (CCPA 1962). Frydman *et al.* also expressly suggest and motivate the selection of a cyclohexyl substitution. For example, cyclopropyl and cyclobutyl groups introduce constraints into otherwise flexible spermine

molecules (col. 4, lines 53-67) and a "cyclohexyl moiety" can be introduced *in a similar manner* to the cyclopropyl and cyclobutyl constraints (col. 5, lines 6-7). The skilled artisan would recognize that the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl series of homologs could be used to evaluate conformational constraints in spermine analogs (*i.e.*, cyclopropyl provides the most constraint whereas cyclohexyl provides the least constraint). As such, making cyclopentyl and cyclohexyl substituted spermine analogs having the same substituents as the explicitly disclosed cyclopropyl and cyclobutyl analogs would be the next logical step.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to also make the cyclopentyl- and cyclohexyl-substituted compounds and to formulate them into pharmaceutical compositions. This is especially true given the limited number of cycloalkyl substituents contemplated in Frydman *et al.* (*i.e.*, cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl). Two of these four cycloalkyls were exemplified in the reference. Accordingly, the skilled artisan would have been highly motivated to choose the instantly claimed cyclohexyl substitution, based on the reasonable expectation that structurally similar species usually have the same properties. See, *e.g.*, *Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. See also *Deuel*, 51 F.3d at 1558, 34 USPQ2d at 1214 ("Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.").

(10) Response to Argument

Appellant's arguments have been fully and carefully considered, but fail to be persuasive.

Firstly, with regard to the 35 U.S.C. 112, 1st Paragraph rejection of claims 1-6 as lacking written support for the *proviso* excluding the *trans* isomers of the second excluded compound, CHX(4,4,4-*trans*), Appellants argue that that it is a well settled rule of law that before an applicant can insert a "negative proviso" in a claim, it must be clear that the inventor had "possession of the invention" within the meaning of 35 U.S.C. 112, first paragraph. Appellants cite *In re Johnson* as supporting case law. It is the position of Appellants that the Examiner's reasoning is based on the premise that a disclosure must provide *in haec verba* support for the subject matter of a negative limitation in the claim. However, contrary to Appellant's assessment of the Examiner's position, it is the position of the Examiner not that Appellant's must have provided explicit disclosure of the excluded compound, but that Appellants have failed to disclose a representative number of species within the claimed genus that would provide even implied support for the claimed negative proviso excluding CHX(4,4,4-*trans*) from the claims. The Examiner's position is supported by *In re Johnson*, 194 USPQ 187 (CCPA 1977), wherein the court noted, "[t]he notion that one who fully discloses, and teaches those skilled in the art how to make and use, a genus **and numerous species therewithin**, has somehow failed to disclose, and teach those skilled in the art how to make and use, that genus minus two of those species, and has thus failed to satisfy the requirements of 112, first paragraph, appears to result from a hypertechnical application of legalistic prose relating to that provision of the statute." 194 USPQ at 196 (emphasis added). Appellants, citing the same passage of *Johnson*, conclude that *Johnson* holds that the "disclosure of a genus is sufficient to support a claim to the genus minus

included species" (see Brief at page 5, second full paragraph). The Examiner disagrees. In *Johnson*, the inventors in the parent 1963 application disclosed *in haec verba* a genus of polymers as defined by a general formula and further named some fifty specific dihydric dinuclear phenol compounds which could be used as precursors in the synthesis of the disclosed polymers. The application further contained twenty-six examples of polyarylene polyethers (*i.e.*, species within the disclosed genus). Two of the species explicitly disclosed in the 1963 application, designated as species [1] and species [2] in *Johnson*, were excluded via a negative proviso in a continuation-in-part application (the 1972 application). The court in *Johnson* reversed the 35 U.S.C. 112, 1st paragraph rejection of the claims to a limited sub-genus on the basis that that the parent case clearly described a genus of polymers, described fifty specific choices for the precursor compound, and provided twenty-six examples which detail fifteen species of polyarylene polyethers. The fact pattern in the instant case is not the same as that in *Johnson*. Here, rather describing a genus and "numerous species" within the genus, Appellants describe a genus and one specie within the genus (*i.e.*, the first compound recited following the negative proviso in claim 1). The Examiner believes the present fact pattern to be more closely related to that in *In re Welstead*, 59 CCPA 1105, 463 F.2d 1110, 174 USPQ 449 (1972), wherein the applicant in *Welstead* was attempting to introduce into his claims a new subgenus where the specification contained neither a description of the subgenus nor a description of the species thereof. This is inapposite to applicants in *Johnson*, whose specification contained a broad and generic disclosure, coupled to extensive examples fully supportive of the limited genus applicants were then claiming. In view of both *Johnson* and *Welstead*, the Examiner maintains that Appellant's broad disclosure of a genus, coupled to a disclosure of one specie within that

genus, does not provide support for the exclusion of the compound CHX(4,4,4-*trans*) (*i.e.*, the second compound recited after the negative proviso in claim 1).

Secondly, with regard to the 35 U.S.C. 112, 1st Paragraph rejection of claims 1-6 as introducing new matter with respect to the definition of Q, wherein Q is defined as "a cycloalkyl group having from 5 to 10 carbon atoms", Appellants argue that this rejection appears identical in nature to the "written description" of claims 1-6 regarding the claimed negative proviso. As such, Appellants argue that if the negative proviso discussed above is appropriate then the present limitation that effectively excludes compounds embraced by the same generic disclosure is also appropriate for the reasons discussed above. The Examiner disagrees and refers to the rebuttal discussed supra. The Examiner maintains that disclosure of Q substituents having cycloalkyl groups from 3 to 10 carbon atoms, coupled to the explicit disclosure of a single compound having a Q substituent comprising a 6 carbon atom cycloalkyl group, does not provide written support for the claimed "a cycloalkyl group having from **5** to 10 carbon atoms". Nowhere do Appellants disclose a specie wherein Q is a 5 carbon atom cycloalkyl group. As such, there is no support for the lower limitation of a 5 carbon atom cycloalkyl group as recited in the instant claims.

Thirdly, and lastly, with respect to the 35 U.S.C. 103 rejection of claims 1-6 as being obvious over Frydman et al. (USP No. 5,889,061), Appellants do not appear to dispute the fact that Frydman et al. obviate the claimed compounds or compositions comprising the claimed compounds. Rather, Appellants argue that the Examiner's rejection of the claims over the cited prior art requires that the limitation in the body of the claims that the composition contain "an amount effective" to produce an "anti-diarrheal or gastrointestinal anti-spasmodic" action be

ignored. However, contrary to Appellant's characterization of the rejection, the Examiner does not ignore this claim limitation. Rather, the term "effective amount" as recited in the instant claims is interpreted in light of the specification, which states at page 10 that a "suitable dose of agent will lie in the range of about .0001 mg to about 500 mg per kilogram of mammal body weight being treated". This is a 5 x 10^6 fold range of doses. Frydman *et al.* teach compounds encompassed by the claimed genus and teaches that such compounds can be formulated into pharmaceutical compositions for the treatment of cancer (col. 21, line 5 to col. 22, line 2). Frydman *et al.* teach that the pharmaceutical unit dosage chosen is preferably fabricated and administered to provide a concentration of drug at the point of contact with the cancer cell of from 1 μM to 10 μM, preferably from 1 to 100 μM (col. 22, lines 3-7). It would be obvious to one skilled in the art that a composition comprising a compound of Frydman *et al.* to provide a concentration of 1 to 100 μM of compound at the point of contact with a cancer cell when administered to a patient will contain "an effective amount" ranging from about 0.0001 to about 500 mg per kilogram of mammal body weight being treated. As such, the claimed "effective amount" to produce an "anti-diarrheal or gastrointestinal anti-spasmodic" action is not being ignored by the Examiner. Rather, given the broadness of doses defined in the specification, which encompass at least a 5 x 10^6 fold range of doses (i.e., *about* 0.0001 to *about* 500 mg/kg), compositions comprising a compound of Frydman *et al.* for use in the treatment of cancer will necessarily contain an amount of compound falling somewhere within this extremely broad range.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614

Conferees:

/James D Anderson/

Examiner, Art Unit 1614

/Johann R. Richter/

Supervisory Patent Examiner, Art Unit 1616